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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,824	11/07/2001	Fernand Labrie	P/1259-636	4181

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/052,824	Applicant(s) LABRIE, FERNAND	
	Examiner Shaojia A. Jiang	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *7-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 13-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on August 27, 2002 in Paper No. 6 wherein claims 6, 13, and 17 have been amended. Currently, claims 1-28 are pending in this application.

As indicated in the previous Office Action dated May 21, 2002 claims 7-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

The claims have been examined insofar as they read on the elected specie.

Applicant's amendment filed on August 27, 2002 in Paper No. 6 with respect to the rejection of claims 6 and 13-19 made under 35 U.S.C. 112 second paragraph for the use of the indefinite expressions, i.e., expressions " R100 is a bivalent moiety....B-ring by.. " in claim 13 and espressions "HMR3339, EM-800, and EM-1520" in claims 6 and 17, of record in the Office Action dated May 21, 2002 have been fully considered and found persuasive to remove the rejection as to claim 6 and 13-19 since these expressions have been removed from the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, for the use of the indefinite expressions, "an androgenic agent" in claim 3, of record in the Office Action dated May 21, 2002.

Applicant's remarks filed on August 27, 2002 in Paper No. 6 with respect to this rejection made under 35 U.S.C. 112 second paragraph have been fully considered but they are not deemed persuasive to remove the rejection. As discussed in the previous Office Action, the expression "an androgenic agent" in claim 3 renders claim 3 indefinite as failing to clearly set forth the metes and bounds of the patent protection desired. The specification herein fails to set forth the metes and bounds of "an androgenic agent". Moreover, the specification herein fails to provide sufficient working examples to support the broad use of any compound that acts as an androgen or any "androgenic agent" in the claimed method. Therefore, the scope of claims is indefinite as to the composition encompassed thereby employed in the claimed method herein.

The following is new ground rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-6 and 13-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Labrie (5,362,720), and Labrie et al. (WO 96/26201), and Applicant's admission regarding the prior art in the specification at 2 lines 3-4.

Labrie (5,362,720) teaches that estrogens such as 17β-estradiol are well known to be used in estrogen therapy in menopausal women. However, estrogens are known to induce estrogen-dependent diseases such as breast cancer. Labrie also discloses that androgenic compounds or androgenic steroids are useful in methods of treating or preventing estrogen-dependent diseases such as breast cancer. See abstract, col.1 line 35-38, col.4 lines 45-48, col.10, and claims 1-30.

Labrie et al. (WO 96/26201) discloses that the particular SERM, EM-652 (the instant elected species) or its pharmaceutically acceptable salts such as EM-652.HCl, have anti-estrogen activities and are therefore useful in methods of treating estrogen sensitive or estrogen-dependent diseases such as breast cancer, which is known estrogen-induced effects. See abstract, page 1, page 6-8, 10, and 19-21, and claims 11-12.

Applicant's admission regarding the prior art in the specification at 2 lines 3-4 teaches that Hormone Replace Therapy (e.g., administration of estrogens) is known to be useful in treatment of menopausal symptoms.

The prior art does not expressly disclose the employment of the combination of an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, or maybe further combining an androgenic compound in a method of reducing or eliminating the incidence of menopausal symptoms.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ of the combination of an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, or to further combine an androgenic compound in a method of reducing or eliminating the incidence of menopausal symptoms.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the combination of an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, or to further combine an androgenic compound in a method of reducing or eliminating the incidence of menopausal symptoms, since estrogens such as 17β-estradiol is well known in the art to be used in estrogen therapy or Hormone Replace Therapy in menopausal women for reducing or eliminating the incidence of menopausal symptoms. Moreover, 17β-estradiol in combination with androgenic compounds or androgenic steroids is known to be capable to inhibiting breast tumor or cancer growth, and are therefore useful in methods of treating estrogen-dependent diseases, e.g., breast cancer according to Labrie. Further, the particular SERM, EM-652.HCl, is known to be in methods of treating estrogen-dependent diseases. Therefore, one of ordinary skill in the art would have reasonably expected that combining an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, or further combining an androgenic compound would be useful in reducing or eliminating the incidence of menopausal symptoms, while reducing the risk of or treating estrogen-dependent diseases such as breast cancer induced by estrogens during estrogen therapy in menopausal women for reducing or eliminating the incidence of menopausal

symptoms, since each of components herein is known to be useful in the same treatment, i.e., treating estrogen-dependent diseases.

Since all active composition components herein are known to useful to reduce or treat estrogen-dependent diseases, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the teachings of the prior art.

Applicant's remarks filed on August 27, 2002 in Paper No. 6 with respect to this rejection of claims 1-6 and 13-28 made under 35 U.S.C. 103(a) as being unpatentable over Labrie (5,362,720), and Labrie (5,550,107), and Labrie et al. (WO 96/26201), and Applicant's admission regarding the prior art in the specification at 2 lines 3-4, of record stated in the Final Office Action dated May 21, 2002 have been fully considered and but are not deemed persuasive as to the nonobviousness of the claimed method in view of the new ground(s) of rejection above.

Additionally, Applicant's argument that Labrie '720 does not teach that 17β-estradiol is used in estrogen therapy in menopause women, is not found persuasive since Labrie clearly teaches that "[t]he incidence of endometrial cancer increase after menopause, especially in women receiving estrogen therapy without simultaneous treatment with progestins." (see col.1 line 35-38). Moreover, 17β-estradiol is a well

known estrogen to be used in estrogen therapy. Thus, 17β-estradiol as an estrogen is known to be administered to menopause women in estrogen therapy.

Therefore, motivation to combine the teachings of the prior art to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Labrie (5,362,720), and Labrie (5,780,460, PTO-892), and Labrie et al. (WO 96/26201), and Applicant's admission regarding the prior art in the specification at 2 lines 3-4.

Labrie (5,362,720) teaches that estrogens such as 17β-estradiol are well known to be used in estrogen therapy in menopausal women. However, estrogens are known to induce estrogen-dependent diseases such as breast cancer. Labrie also discloses that androgenic compounds or androgenic steroids are useful in methods of treating or preventing estrogen-dependent diseases such as breast cancer. See abstract, col.1 line 35-38, col.4 lines 45-48, col.10, and claims 1-30.

Labrie (5,780,460) discloses that sex steroid precursors such as DEHA alone or in combination with an estrogen are useful in method of reducing or eliminating the incidence of menopausal symptoms, e.g., vaginal atrophy and diminished libido, and also useful in methods of treating or preventing estrogen-dependent diseases such as breast cancer. See abstract, col. 1-2, col.3 lines 44-55, and claims 1-2.

Labrie et al. (WO 96/26201) discloses that the particular SERM, EM-652 (the instant elected species) or its pharmaceutically acceptable salts such as EM-652.HCl, have anti-estrogen activities and are therefore useful in methods of treating estrogen sensitive or estrogen-dependent diseases such as breast cancer, which is known estrogen-induced effects. See abstract, page 1, page 6-8, 10, and 19-21, and claims 11-12.

Applicant's admission regarding the prior art in the specification at 2 lines 3-4 teaches that Hormone Replace Therapy (e.g., administration of estrogens) is known to be useful in treatment of menopausal symptoms.

The prior art does not expressly disclose the employment of the combination of an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, and DHEA in a method of reducing or eliminating the incidence of menopausal symptoms.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ of the combination of an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, and DHEA in a method of reducing or eliminating the incidence of menopausal symptoms.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the combination of an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, and DHEA in a method of reducing or eliminating the incidence of menopausal symptoms, since estrogens such as 17β-estradiol are well known in the art to be used in estrogen therapy or Hormone Replace Therapy in menopausal women for reducing or eliminating the incidence of menopausal symptoms. Moreover, sex steroid precursors such as DEHA alone or in combination with an estrogen (e.g.,17β-estradiol) is known to be useful in method of reducing or eliminating the incidence of menopausal symptoms, and also useful in methods of treating or preventing estrogen-dependent diseases such as breast cancer according to Labrie. Androgenic compounds are also known to be useful in methods of treating estrogen-dependent diseases. Further, the particular SERM, EM-652.HCl, is known to be in methods of treating estrogen-dependent diseases. Therefore, one of ordinary skill in the art would have reasonably expected that combining an estrogen such as 17β-estradiol and the particular SERM, EM-652.HCl, and DHEA, or further combining an androgenic compound would be useful in reducing or eliminating the incidence of menopausal symptoms, while reducing the risk of or treating estrogen-dependent diseases such as breast cancer induced by estrogens during estrogen therapy in menopausal women for reducing or eliminating the incidence of menopausal symptoms, since each of components herein is known to be useful in the same treatment, i.e., treating estrogen-dependent diseases.

Since all active composition components herein are known to useful to reduce or treat estrogen-dependent diseases, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the teachings of the prior art.

Applicant's testing results in Example 1-2 and 4-5 of the specification at pages 42-53 and 60-73 have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed invention but are not deemed persuasive for the following reasons. The results herein are not seen to provide clear and convincing evidence of nonobviousness or unexpected results over the cited prior art for the combination of 17β-estradiol and EM-652.HCl, or the combination of 17β-estradiol and EM-652.HCl and DHEA in the claimed method of reducing or eliminating the incidence of menopausal symptoms. The specification provides no side-by-side comparison with the closest prior art.

Moreover, the testing herein is merely in the treatment of bone loss, a single menopausal symptom, in female rats, (see page 68-69). Thus, the evidence in the testing on is not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed broad range of menopausal symptoms herein. See MPEP § 716.02(d). Additionally, the tests herein merely employ two particular SERMs

(i.e., EM-652 and EM-800), particular estrogens, and particular androgenic agents. Again, the evidence in the testing is not commensurate in scope with the claimed invention and does not demonstrate criticality of the claimed range of active agents herein in the claimed method. Further, the specification provides no evidence for treating menopausal women.

Therefore, no clear and convincing evidence of nonobviousness or unexpected results for the combination in the claimed method presented in specification herein is seen to support the nonobviousness of the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a).

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

Shaojia A. Jiang, Ph.D.
Patent Examiner, AU 1617
November 6, 2002

SREENI PADMANABHAN
PRIMARY EXAMINER

11/16/02